nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☑	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☑	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☑	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☑	A description of all covariates tested
☑	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☑	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☑	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☑	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☑	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☑	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Western blots were obtained by regular film developing and the digital chemiluminescent detector Azure 280. Immunofluorescence, Immunohistochemistry images were captured on Keyence microscope (BZ-X710). Absorbance, luminescence and fluorescence assays were measured with a ClarioSTAR (BMG Labtech) microplate reader.
Data analysis	ImageJ (versions 1.51 and 1.54j) and Photoshop (version 23.5.2) overlay method were used to contrast and overlay images as described in the Methods section. ImageJ was used to perform densitometry analysis and staining quantifications. All data analysis was finalized using excel (16.54) and Graphpad Prism 9.0.0.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Source data are provided in this paper. All generated or analyzed data during this study are included in this published article (and its Supplementary Information files).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All patients samples were age matched and randomly selected.
Reporting on race, ethnicity, or other socially relevant groupings	Four cases of PSC and three cases of PBC human liver specimens obtained from liver biopsy from 2014-2019, and five normal liver tissues obtained from surgical resection for patients suffering from intrahepatic ductal stones from 2018-2019 were obtained from the department of Pathology at the Xiangya Hospital Center South University, Changsha, Human province, China.
Population characteristics	All patients samples were randomly selected.
Recruitment	There was no bias in the selection of patients. The sex of the participants was self-reported, and neither sex, gender, race nor ethnicity was considered during participant selection.
Ethics oversight	The research was conducted under both the Declarations of Helsinki and Istanbul, and the study protocol was approved by the IRB and the Medical Ethical Committee of Xiangya Hospital Central South University.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☑ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A reasonable sample size was estimated from similar experiments in others' and our former publications to ensure adequate reproducibility of results. The exact n values used to calculate the statistics are provided.
Data exclusions	No data were excluded from analysis.
Replication	All experiments were performed independently 3 times unless stated differently in the figure legend. All attempts at replication were successful under the experimental conditions defined.
Randomization	Animals with similar age and weight were randomly allocated to experimental groups. For in vitro experiments, cultures were randomly chosen for different treatments and experiments were performed multiple times.
Blinding	Investigators were blinded to group allocation during data collection and /or analysis.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	N/A
Research sample	N/A
Sampling strategy	N/A
Data collection	N/A
Timing	N/A
Data exclusions	N/A
Non-participation	N/A
Randomization	N/A

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	N/A
Research sample	N/A
Sampling strategy	N/A
Data collection	N/A
Timing and spatial scale	N/A
Data exclusions	N/A
Reproducibility	N/A
Randomization	N/A
Blinding	N/A

Did the study involve field work? ☐ Yes ☑ No

Field work, collection and transport

Field conditions	N/A
Location	N/A
Access & import/export	N/A
Disturbance	N/A

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☑ Antibodies
☐	☑ Eukaryotic cell lines
☑	☐ Palaeontology and archaeology
☐	☑ Animals and other organisms
☑	☐ Clinical data
☑	☐ Dual use research of concern
☑	☐ Plants

Methods

n/a	Involved in the study
☑	☐ ChIP-seq
☑	☐ Flow cytometry
☑	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Anti-FOXM1 (Abcam, ab207298; Genetex, GTX55627), anti-MATα2 (Proteintech, 55309-1-AP; Proteintech 15952-1-AP and 2B7G8), anti-MAT2β (Novus Biologics, BNP1-82797; Genetex, GTX50027), anti-α-SMA (Abcam, ab5831), anti-COL1A1 (Abcam, ab270993), anti-β-actin (Abcam, ab8226), anti-F4/80 (Abcam, ab300421), anti-SMAD3 (Rockland, 600-401-920), anti-pSMAD3 (Rockland, 600-401-C48), anti-TNF alpha (Abcam, ab183218), anti-Tubulin (Abcam, ab15568), anti-IL-6 (Abcam, ab259341), and H3 (Abcam, ab18521). For WB a 1:1000 dilutions were used, for IF and IHC, 1:200 dilutions were used. Details are avilable in Supplementary information file and Methods section.
Validation	All antibodies with their catalog number and company were listed in Supplementary Table 2. Also, all antibodies were validated in our previous work (Yan Li, 2020)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	LX-2 (Human) cells were obtained from Dr. Ekihiro Seki and RAW 264.7 cells (Mouse,TIB71 TM) were obtained fron American Type Culture Collection (Rockville, MD)
Authentication	Cell lines were authenticated in 2020 by STR testing and all cells were good to use. No contamination were detected.
Mycoplasma contamination	Both cell lines were tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Palaeontology and Archaeology

Specimen provenance	N/A
Specimen deposition	N/A
Dating methods	N/A

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Foxm1fl/fl, Alb-Cre, and Clec4f-Cre mice (C57BL/6 background) were purchase from Jackson Laboratory. Lrat-Cre transgenic mice (kindly provided by Dr. Robert Schwabe, Columbia University) and an cross bred to generate transgenic mice of different genotype. Foxm1 flox mice were used as WT controls.
Wild animals	N/A
Reporting on sex	Male mice of same age group (random selection, 3-4 months-old) were used for all experiment in the study. Males were used because they are more sensitive to liver fibrosis.
Field-collected samples	No field collected samples used in this study.
Ethics oversight	All procedure protocols, use and the care of the animals were reviewed and approved by the Institutional Animal Care and Use Committee at Cedars Sinai Medical Center. Experiments on mice were approved by the Institutional Animal Care and Use Committee of CSMC (No. 8850).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A
Study protocol	N/A
Data collection	N/A
Outcomes	N/A

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☑	☐	Public health
☑	☐	National security
☑	☐	Crops and/or livestock
☑	☐	Ecosystems
☑	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☑	☐	Demonstrate how to render a vaccine ineffective
☑	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☑	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☑	☐	Increase transmissibility of a pathogen
☑	☐	Alter the host range of a pathogen
☑	☐	Enable evasion of diagnostic/detection modalities
☑	☐	Enable the weaponization of a biological agent or toxin
☑	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	
Files in database submission	
Genome browser session (e.g. UCSC)	

Methodology

Replicates	
Sequencing depth	
Antibodies	
Peak calling parameters	
Data quality	
Software	

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	
Instrument	
Software	
Cell population abundance	
Gating strategy	

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	
Design specifications	
Behavioral performance measures	

Imaging type(s)	
Field strength	
Sequence & imaging parameters	
Area of acquisition	

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	
Normalization	
Normalization template	
Noise and artifact removal	
Volume censoring	

Statistical modeling & inference

Model type and settings	
Effect(s) tested	

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

(See Eklund et al. 2016)

Correction

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Graph analysis

Multivariate modeling and predictive analysis